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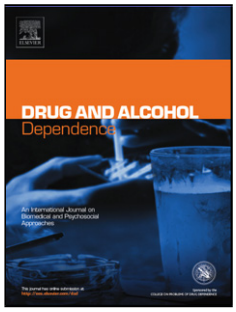

Title: Naloxone without the needle − systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal

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Naloxone without the needle – systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal

Running head: Systematic review: routes for non-injectable naloxone

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Highlights

- Deaths from opioid overdose can be prevented by prompt injection of the opiate antagonist naloxone
- After 40 years of injection-based naloxone, a concentrated naloxone nasal spray is now approved
- Systematic review finds 3 potential injection-free naloxone routes: nasal, sublingual & buccal
- Alongside concentrated nasal naloxone, buccal may have distinct advantages as future product
- Wider pre-provision of naloxone across the community is essential; all three routes warrant study

Abstract

Introduction: Deaths from opioid overdose can be prevented through administration of the antagonist naloxone, which has been licensed for injection since the 1970s. To support wider availability of naloxone in community settings, novel non-injectable naloxone formulations are being developed, suitable for emergency use by non-medical personnel. **Objectives:** 1) Identify candidate routes of injection-free naloxone administration potentially suitable for emergency overdose reversal; 2) consider pathways for developing and evaluating novel naloxone formulations. **Methods:** A three-stage analysis of candidate routes of administration was conducted: 1) Assessment of all 112 routes of administration identified by FDA against exclusion criteria. 2) Scrutiny of empirical data for identified candidate routes, searching PubMed and WHO International Clinical Trials Registry Platform using search terms “naloxone AND [route of administration]”. 3) Examination of routes for feasibility and against the inclusion criteria. **Results:** Only three routes of administration met inclusion criteria: nasal, sublingual and buccal. Products are currently in development and being studied. Pharmacokinetic data exist only for nasal naloxone, for which product development is more advanced, and one concentrated nasal spray was granted licence in the US in 2015. However, buccal naloxone may also be viable and may have different characteristics. **Conclusion:** After 40 years of injection-based naloxone treatment, non-injectable routes are finally being developed. Nasal naloxone has recently been approved and will soon be field-tested, buccal naloxone holds promise, and it is unclear what sublingual naloxone will contribute. Development and approval of reliable non-injectable formulations will facilitate wider naloxone provision across the community internationally.

KEYWORDS: naloxone; drug development; heroin; opioid; overdose; deaths; nasal; buccal; sublingual.

1. INTRODUCTION

1.1. An excess of deaths

Heroin/opioid overdose deaths represent a major international public health concern (UNODC/WHO, 2013). Even in countries with low prevalence of opioid use relative to consumption of other illicit drugs, opioids contribute disproportionately to overdose fatalities (Degenhardt et al., 2011; WHO, 2014). In the United States (US), there has been a greater than fourfold increase in overdose deaths from prescription opioids since 1999, accounting for 16,651 deaths in 2010 alone (CDC, 2012; Volkow et al., 2014), as well as a simultaneous rise in heroin overdose deaths from 2007 onwards (Calcaterra et al., 2013). In the United Kingdom (UK), a 64% rise in heroin/morphine deaths was recorded for England and Wales between 2012 and 2014 (ONS, 2015).

1.2. Wider provision of naloxone

In response, there are increasing calls for wider access to the opioid antagonist naloxone (ACMD, 2012; UNODC/WHO, 2013). The World Health Organization (WHO) launched new guidelines on the prevention of opioid overdose deaths in 2014, recommending that “people likely to witness an opioid overdose should have accesss to naloxone” (p. x) (WHO, 2014).

In the US, the National Institute on Drug Abuse (NIDA) made funding available for the development of novel injection-free naloxone products (Volkow et al., 2014) and, in November 2015, the US Food and Drug Administration (FDA) gave approval to a new nasal spray of concentrated naloxone solution (FDA, 2015), thereby giving the first regulatory product approval world-wide for a non-injectable naloxone product.

1.3. The promise of non-injectable naloxone

The notion of non-injectable formulations of naloxone is attractive: naloxone without needles would have many advantages. Firstly, medications which need to be injected are intimidating for laypersons to use in non-medical settings (Beletsky et al.,

2012). Secondly, with use of naloxone by injection, there is the risk of needle-stick injury and contraction of blood-borne diseases (e.g., hepatitis C, HIV), which are highly prevalent among this patient group. Thirdly, non-injectable naloxone could more easily be provided to a much wider intervention workforce (e.g., hostel staff, outreach workers, police, etc.).

New methods of delivery for naloxone need to be suitable for emergency use by non-medical personnel in community-based settings. Furthermore, formulations should be developed with longer shelf-life, especially in view of the pre-placement of these naloxone products to community and families and other non-hospital settings. Naloxone also needs to be absorbed rapidly, given the emergency situation, in quantity sufficient to effect quick reversal of opioid-induced respiratory depression.

The reference for any candidate non-injectable routes is injectable naloxone, administered by the licensed intramuscular (IM), intravenous (IV), and subcutaneous (S/C) routes (WHO, 2014). When administered by the IM or S/C routes, naloxone typically reverses opioid action within 3-7 minutes; whereas the effect from IV administration has an onset typically within 2 minutes (UNODC/WHO, 2013). With long-standing approval for, and experience with, naloxone in injectable form, this sets the standard against which possible non-injectable formulations need to be measured (Hertz, 2012). In this review, we examine the options for non-injectable naloxone with potential application for wider community-based opioid overdose reversal.

2. MATERIAL AND METHODS

A three-stage approach has been taken (see Figure 1). The first stage was an examination of all 112 routes of drug administration listed by the US Food and Drug Administration (FDA, 1992)updated 2014). For each of the 112 possible routes of administration, we considered the potential applicability as a viable non-injectable route for emergency naloxone delivery by non-medical personnel (see

Supplementary Material[1]). We thus identified routes as unsuitable according to five exclusion criteria:

i) if the drug administration is by injection (or similar invasive procedure);

ii) if the route is only relevant to medical procedures or requires medical training;

iii) if the route is not publicly acceptable for administration by non-medical bystanders (e.g., rectal or vaginal administration);

iv) if the route does not produce adequate systemic drug concentrations;

v) if the route does not produce sufficiently rapid drug absorption relative to parenteral administration (Hertz, 2012).

The second stage was to systematically search PubMed and the WHO International Clinical Trials Registry Platform for the potential candidate routes of administration that had emerged from the first stage. The search term “naloxone AND [route of administration]” (e.g., “naloxone AND (nose OR nasal OR intranasal)”) was used for each route across the electronic databases (see Supplementary Material[2] for search protocol). R.M. conducted the search and assessed retrieved studies for eligibility under supervision of J.S. Relevant original research studies that were published in English language and reported on the outcomes of in vivo naloxone administration (e.g., overdose reversals, pharmacokinetics/-dynamics data) in humans or animals were included in our analysis (see Figure 2 for PRISMA diagram).

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:...

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The third stage, for remaining potential non-injectable routes of administration, comprised a more rigorous examination of the evidence against the inclusion criteria (see also Table 1):

i) the route is suitable for overdose emergency situation;

ii) the route does not bear major risk of compromise from overdose complication.

For the first and third stage, R.M. and J.S. used the specified exclusion and inclusion criteria to independently screen all relevant routes of administration for potential inclusion. When the reviewers reached different decisions, B.F. acted as the final arbitrator for inclusion or exclusion of a route.

3. RESULTS

3.1. Shortlisting potential non-injectable routes from analysis of all routes of administration

From examination of all 112 listed routes of administration (FDA, 1992), four were excluded on the basis that they held no analytic relevance ('unassigned', 'unknown', 'other' and 'not applicable'). From the remaining 108 categories, a further 102 were excluded according to the criteria listed in 'Method' (see determination in Supplementary Material[3]). For instance, enteral delivery (through the gastro-intestinal mucosa) was excluded because of insufficient systemic absorption, since naloxone is poorly bioavailable if swallowed due to high first-pass metabolism (Fishman et al., 1973). After this process, six non-injectable candidate routes remained to be considered further (see Table 1).

We then removed two of these six routes (see in italics at bottom of Table 1) on the basis that they were overarching categories of routes already being considered. Thus 'oropharyngeal' was removed as substantially overlapping with

[3] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:...

'buccal' and 'sublingual', and 'transmucosal' was removed and considered under the specific mucosa ('buccal', 'intranasal', 'sublingual'). With regard to the wider range of possible transmucosal routes, rectal delivery, which has replaced administration by injection for several emergency medications in paediactric care (Lyon and McIntosh, 1985; NICE, 2009), was specifically not included for further consideration since it is unlikely to be acceptable to family and peers for community-based naloxone emergency administration to overdose victims.

3.2. Fuller examination of the four shortlisted potential non-injectable routes

We next examined more fully these four potential routes (buccal, nasal, sublingual, respiratory/inhalation) based on the literature retrieved from the electronic databases. According to the WHO International Clinical Trials Registry Platform, nasal naloxone is currently being investigated in clinical trials by the Norwegian University of Science and Technology (NCT02307721, NCT01939444), in the US by the University of Cincinatti (NCT01912573) and Lightlake Sinclair Ltd. (NCT01567670), in Jordan by Mitovie Pharma Ltd (NCT01622504), and in Australia at the Sydney Medically Supervised Injecting Centre (ACTRN12611000852954). Buccal naloxone is currently being studied at King's College London in the UK (EudraCT 20140001802-16 & 2016-000582-23; see below). No database entries were found for study of naloxone via the sublingual or respiratory/inhalation routes.

We then consider each of these in turn:

3.2.1 Respiratory (inhalation). We excluded the 'Respiratory (Inhalation)' route as not being suitable for further consideration because the victim might no longer be breathing (or breathing only very shallowly). Further, current portable devices for drug delivery to the lungs could not be used reliably in an emergency situation by non-medical personnel (spray or aerosolized naloxone is better considered under the 'nasal' category).

3.2.2 Sublingual. For the sublingual route, PubMed identified one pharmacodynamics study in opioid-dependent volunteers, where sublingual naloxone precipitated withdrawal symptoms in 5 out of 9 participants (Preston et al., 1990). Apart from separate work on buprenorphine/naloxone combination, no further investigative work for sublingual was identified.

3.2.3 Nasal. PubMed search yielded 18 studies reporting in vivo administration of intranasal naloxone. Preclinical data from rodent studies showed complete absorption of nasal naloxone (bioavailability relative to IV: F% = 101%; Hussain et al., 1984). In first in-human trials, nasal naloxone was found to elicit withdrawal symptoms in opioid-dependent volunteers (Loimer et al., 1992, 1994). Since the early 2000s, nasal naloxone has been used off-label by ambulance personnel (Barton et al., 2005, 2002; Belz et al., 2006; Kelly et al., 2005; Kerr et al., 2009; Merlin et al., 2010; Robertson et al., 2009; Weber et al., 2012) and in the emergency department (Sabzghabaee et al., 2014). More recently, improvised nasal kits (consisting of a pre-filled naloxone syringe and an atomizer which fits onto the syringe to generate a nasal spray) have been provided to opioid users, peers, and families in take-home naloxone trials (Doe-Simkins et al., 2009; Dwyer et al., 2015; Walley et al., 2013a, 2013b), and succesful overdose reversals using improvised nasal kits have also been reported for police first responders (Rando et al., 2015). However, the only published pharmacokinetics study in humans found intranasal naloxone (2mg/5ml) had a relative bioavailability of only 4% (Dowling et al., 2008).

3.2.4 Buccal. PubMed search identified two preclinical studies on buccal naloxone. In rodents, buccal naloxone administration led to high bioavailability (F% = 69-71%) and a T_{max} of 24 minutes (Hussain et al., 1987; Hussain et al., 1988), whereas in dogs, despite buccal T_{max} at 18 minutes, bioavailability was low (16%) (Hussain et al., 1988).

Consequently, only three routes of administration are carried forward for full consideration as candidate routes of administration for emergency naloxone by non-medical personnel: nasal, sublingual and buccal. We now compare all three routes more fully against the FDA-identified reference route (injectable naloxone) (Hertz, 2012).

3.3. Testing requirements for potential new routes of administration (nasal, sublingual and buccal)

For all three identified candidate non-injectable routes (nasal, sublingual and buccal), investigators and manufacturers need to consider the FDA guidance on development of novel naloxone formulations for outpatient use (Hertz, 2012). The FDA proposed this strategy mindful of the good safety profile of naloxone: while naloxone blocks opiate receptors, it has no pharmacological effect in individuals who are not opiate-dependent and do not have any opioids in their system. Moreover, as it has no potential of abuse due to lack of euphoriant effect (Brunton, 2010), the pharmacokinetics of novel naloxone formulations can thus be safely tested in healthy volunteers. According to the FDA guidance (Hertz, 2012), pharmacokinetic studies will need to "[e]valuate the relative bioavailability of at least two different doses compared to parenteral injection of naloxone (IM, IV or SC). [Studies should] [c]ompare a parenteral dose of naloxone of at least 0.4 mg to dose(s) of the new product that would be expected to result in similar or greater drug exposure. Target plasma naloxone levels [should be] detectable in all subjects for a meaningful duration comparable to approved product.".

The FDA guidance (Hertz, 2012) outlines the following key questions concerning the bioavailability and usability of a new product:

1) "If the relative bioavailability is low, will there be adequate efficacy? If the relative bioavailability is high, are there implications for the safety profile?"
2) "Can the product be used by the intended population, i.e. [is] administration by someone other than the patient [possible]?"

For all potential non-injectable naloxone products, it will be important to focus on absorption within the first 20-30 minutes. For emergency overdose applications, any novel naloxone product will need to be absorbed rapidly into the bloodstream and thence across the blood-brain barrier. This is plausible for the nasal, buccal and sublingual routes, since they all involve absorption across a mucous membrane outside the gastro-intestinal tract. They drain to the peripheral circulation rather than

the hepatic portal vein, thus avoiding the hepatic portal system and first-pass metabolism in the liver.

The nasal route is characterized by high blood perfusion of the nasal mucosa which facilitates transmucosal absorption, and drainage mainly occurs into the facial veins (Dale et al., 2006; Standring, 2015). The buccal route (from the oral vestibular cavity) and the sublingual route both drain into the internal jugular vein via the facial veins, and thence rapidly to the brain (Standring, 2015).

For nasal drug delivery, an additional nose-to-brain (N2B) connection has been hypothesized. It is mooted that drugs could be transported directly into the cerebrospinal fluid via the olfactory and trigeminal nerves (Djupesland et al., 2014) through the olfactory epithelium (on the roof of the nasal cavity) projecting directly into the olfactory bulb. However, human evidence of direct drug transport from the nose to the cerebrospinal fluid is currently still lacking (Djupesland et al., 2014; Merkus et al., 2003).

In addition to these anatomical and pharmacological factors, we need to consider the context of emergency overdose reversal (e.g., devices need to be portable, accessible, easy to use and also operational on an unconscious supine overdose victim) as well as the physical health of the target population, including potential damage to, or obstruction of, the relevant mucosa.

3.3.1 Intranasal. Clinical reports describe use of improvised nasal naloxone kits which indicate life-saving benefit in many situations (see Results 3.2). However, for non-concentrate nasal kits, there remains uncertainty with regard to the formulation's bioavailability and reliability of clinical effectiveness (Strang et al., 2016). For example, Dowling et al. (2008) found that non-concentrate nasal naloxone spray (2mg/5mL) had a bioavailability of only 4%, although the authors themselves acknowledged that the poor absorption was likely due to the insufficiently concentrated formulation.

In two ambulance-based clinical trials, intranasal naloxone had a substantial non-response rate: among opioid overdose victims, 26% (using 2mg/5mL nasal formulation; Kelly et al., 2005) and 18% (using 2mg/mL nasal formulation; Kerr et al., 2009) required a second rescue dose of naloxone (the second dose given IM).

For a purpose-developed nasal naloxone spray, a more concentrated formulation of naloxone should be used, e.g., at least 5-10x current concentrations, a) to overcome the drug loss associated with administration of excessive volumes to the nasal cavity and b) to administer naloxone across the recommended dose range (i.e. bioequivalent to 0.4-2 mg IV or IM).

A significant positive development in this regard is the recent FDA approval of a new nasal spray formulation of a concentrated naloxone solution (US territory only) (FDA, 2015). Pharmacokinetics data (including dose-equivalence and constancy) on concentrated naloxone nasal spray will hopefully become available and it will be important to field-test the new product to assess the potential significance of practical obstacles, e.g., inter-individual variability, impact of airway blockage or apnea, impact of vomitus in the nasal passages or mouth, impact of nasal mucosal damage from drug abuse. This is necessary because drug users may have damaged nasal mucosa – for example, ulceration, scarring and loss of tissue from repeated cocaine use (Peyrière et al., 2013). Absorption may consequently vary substantially between individuals, making it difficult to achieve systemic drug levels rapidly and reliably. There is also the possibility of interference with nasal absorption from vomiting associated with the overdose, thereby rendering the nasal cavity compromised.

3.3.2 Sublingual: An FDA product application was submitted in 2015 for a sublingual naloxone spray (FDAnews, 2015). If the naloxone were to be absorbed rapidly and efficiently, then this could be viable. However, there are several concerns regarding the suitability of the sublingual route for the emergency administration of naloxone. Access to the mucosa under the tongue may be obstructed if the mouth of the overdose victim is closed and/or if vomiting has occurred. A sublingual spray would

be difficult to administer, as liquid may be lost to swallowing. Sublingual tablets are typically small and would be hard to position. Furthermore, significant inter-subject variability of sublingual naloxone delivery and effect was observed in a pharmacodynamics study in opioid users (Preston et al., 1990).

3.3.3 Buccal: Despite lack of human in vivo data for buccal naloxone, we see merit in exploration of the option of a solid-form rapid-dispersal buccal tablet formulation. Working between the Addictions Department and the Institute of Pharmaceutical Science at King's College London, we have developed a working prototype lyophilised tablet of naloxone, suitable for application to the buccal mucosa with rapid drug release for absorption (e.g., within 30 seconds; Alqurshi et al., submitted). Approval has been received from the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK for a first-in-human CTIMP to investigate buccal delivery of naloxone (EudraCT number 2014-001802-16), and the Phase-I trial will generate pharmacokinetics data of naloxone absorption from the buccal cavity in healthy volunteers. This first study is examining absorption of a buccal liquid, and a subsequent study (EudraCT number 2016-000582-23) will examine absorption from the buccal lyophilized formulation of naloxone which we have developed and manufactured (Alqurshi et al., submitted) and whose pharmacokinetics will be compared to those with IV and IM injection of the existing licensed naloxone. In this way, we will explore dose comparability and draw a comparison between absorption of buccal naloxone from solution and from the new lyophilized formulation.

4. DISCUSSION

The development of non-injectable formulations of naloxone is of major importance because of the potential for administration by non-medical people in emergency situations. Injectable routes work well and are fit for purpose for use by medical staff in hospital settings or by ambulance personnel attending a community emergency overdose scenario. However, the consideration is different for emergency administration by the general public (i.e. without medical training). While family

members can be trained and are regularly given such training and emergency injectable medications for other potential medical crises (e.g., adrenaline/epinephrine for allergy anaphylaxis, insulin for diabetics, etc.), there would nevertheless be greater ease of distribution and comfort with emergency administration if an effective and reliable non-injectable formulation of naloxone was available.

Examination of the extensive list of more than 100 different routes of administration identified three plausible non-injectable routes – nasal, sublingual and buccal - which warrant proper study. If successful, all three routes could become viable, cost-effective future alternatives to the licensed naloxone injection and could facilitate effective bystander response to opioid-overdose while minimizing associated risk.

Consideration and investigation of nasal naloxone is the more advanced area. After a decade of community provision of improvised naloxone nasal spray, several pharmaceutical companies have recently been developing and testing purpose-made naloxone nasal sprays.

In November, 2015, FDA approved a first concentrated naloxone nasal spray (FDA, 2015) and granted fast-track review to a new drug application for a subligual naloxone spray (FDAnews, 2015). In the US at least, the new concentrate nasal product is expected to replace improvised nasal kits which - despite lack of regulatory testing or evidence of bioavailability - had been introduced in growing numbers since the late 2000s.

Sublingual medications have been used in medicine to great benefit in emergency situations, such as glyceryl trinitrate (GTN) sublingual tablets or spray as acute treatment of angina or myocardial infarct. However, the sublingual route may be compromised if there is vomit or secretions.

No human data exist for buccal naloxone to date, and study of the buccal route for naloxone administration is less advanced. However, the buccal route has been successfully used to develop non-injectable versions of other medications

previously available as injection only. Buccal midazolam ('Buccolam') produces rapid onset of action and its bioavailability (80%) is slightly superior to nasal midazolam (73-75%; Dale et al., 2006; Knoester et al., 2002; Schwagmeier et al., 1998; Taylor et al., 2008). Buccolam is now a licensed treatment that parents can administer while awaiting professional medical care (MHRA, 2011). There have also been promising experimental results with buccal naltrexone delivery in humans (Paderni et al., 2013). With regard to feasibility of the three candidate routes (see also Table 1), we consider the nasal route to be strong if concentrated solutions are used and provided dose-titration schedules can be made possible. We consider the sublingual route to be weakest, given that access to the sublingual mucosa may be obstructed in at least two scenarios: a) if the mouth of the overdose victim is closed and/or b) if vomiting has occurred. We consider the buccal route to hold real potential if rapid absorption and good stability can be achieved.

The main strength of this review lies in the methodological approach of its exhaustive consideration of all FDA-recognized routes of administration. However, we cannot rule out the possibility that other non-injectable routes that may in future prove feasible for naloxone administration due to technological advances. The scope of this review is further limited by the lack of empirical data from pre-clinical or clinical studies, which reflects the lack of investment in naloxone product development by science and by the pharmaceutical industry. A particular current failing is the disconnect between clinical innovation and the need for evidence of bioavailability and clinical safety (Strang et al., 2016).

With regard to clinical safety, we suggest that the risk of adverse reactions should be studied for novel formulations. The dosage of any new formulation will need to strike a balance between reversing opioid action without causing severe adverse reactions (Hertz, 2012). Reports of the harm caused by naloxone over-antagonism have been described, and high-dose naloxone formulations with increased risk of over-antagonism may also result in negative attitudes from drug

users, as previously reported (Neale and Strang, 2015). Similar to testing of the maximum tolerated dose in cancer treatment, there may be merit in experimental study conducted with opioid-dependent volunteers in order to establish, in a population closer to the relevant target population, the non-response rate, dose adequacy and the speed with which the novel naloxone formulation reverses central opioid action.

At least one study has been conducted using a vulnerable population (i.e. opioid-dependent prisoners) to assess the pharmacodymanics of nasal naloxone (Loimer et al., 1992). However, utmost importance is necessary in design and conduct of studies in opioid-dependent volunteers with attention to the informed consent procedure to ensure that all interested subjects are properly informed and sufficiently protected from potential harm. Community consultation with service user groups has already been initiated to discuss what potential study designs would be feasible and ethically sound.

At a minimum, any licensed new naloxone product should be carefully monitored for potential side effects and non-response rate once it enters the market, and take-home naloxone recipients should be actively encouraged to report any adverse reactions that may occur.

Deaths from opioid overdose can be prevented through prompt administration of naloxone, and there is increasing pre-provision of naloxone for emergency use by non-medical personnel. However, worldwide, provision is held back by reliance on injectable formulations. From application of the FDA criteria and review of all 112 categories for routes of administration, we identify only three routes of possible non-injectable naloxone administration which meet the FDA criteria: nasal, sublingual and buccal. Improvised nasal naloxone kits have been distributed in many cities, and a first concentrate nasal spray was granted FDA approval in November, 2015, although pharmacokinetic data are still not available in the peer-reviewed domain and inter-individual dose variability needs to be studied. The buccal route may have a different

pharmacokinetic profile and may have the advantage of ease of carriage and administration as well as not being obstructed by opiate-induced vomiting. After 40 years of opioid overdose treatment by naloxone injection, non-injectable naloxone products are finally being explored, and nasal, sublingual and buccal routes of delivery warrant proper exploration and testing.

Contributions:

JS and RM drafted the manuscript. RM conducted the database analyses. AA, BF, DT, and PR contributed to the overall work and further development of the manuscript. All authors approved of the final draft of the manuscript.

Author Disclosures

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No specific funding was sought or secured for the study reported in this paper.

Declaration of Interests:
JS declares that he is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. JS is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. He has also worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments (including naloxone products) from whom he and his employer (King's College London) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Reckitt-Benckiser/Indivior, MundiPharma, Braeburn/MedPace and trial medication supply from iGen. His employer (King's College London) has registered intellectual property on a novel buccal naloxone formulation with which all authors are involved. JS has also been named in a patent registration by a Pharma company as inventor of a concentrated nasal naloxone spray. For a fuller account, see JS's web-page at http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx.
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RM, AA, BF, and PR have no interests to declare except that King's College London (employer of all authors) has registered intellectual property on a novel naloxone formulation with which JS, RM, AA, BF, PR, and DT are involved.

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Figure Captions

Figure 1. Selection process of candidate routes of administration.

Figure 2. PRISMA flow diagram of study selection process.

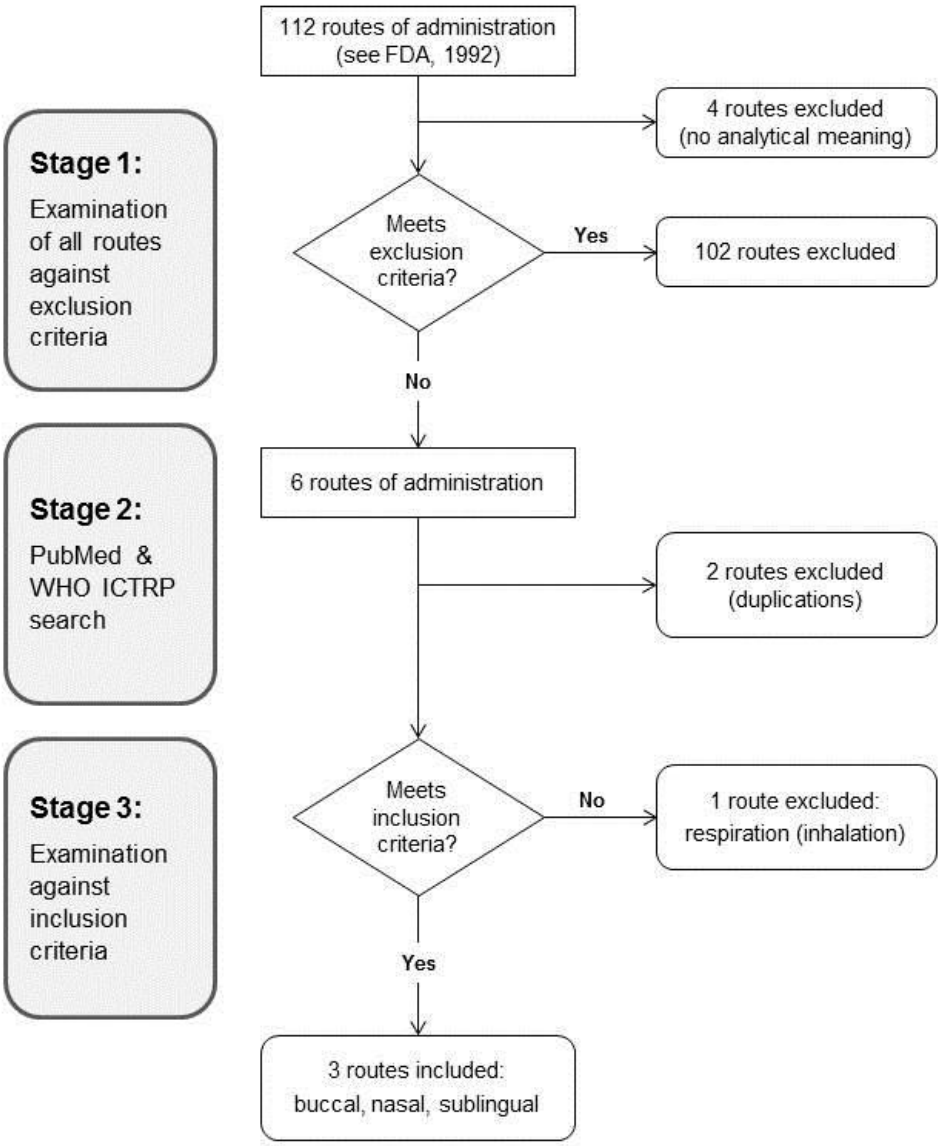

Figure 1

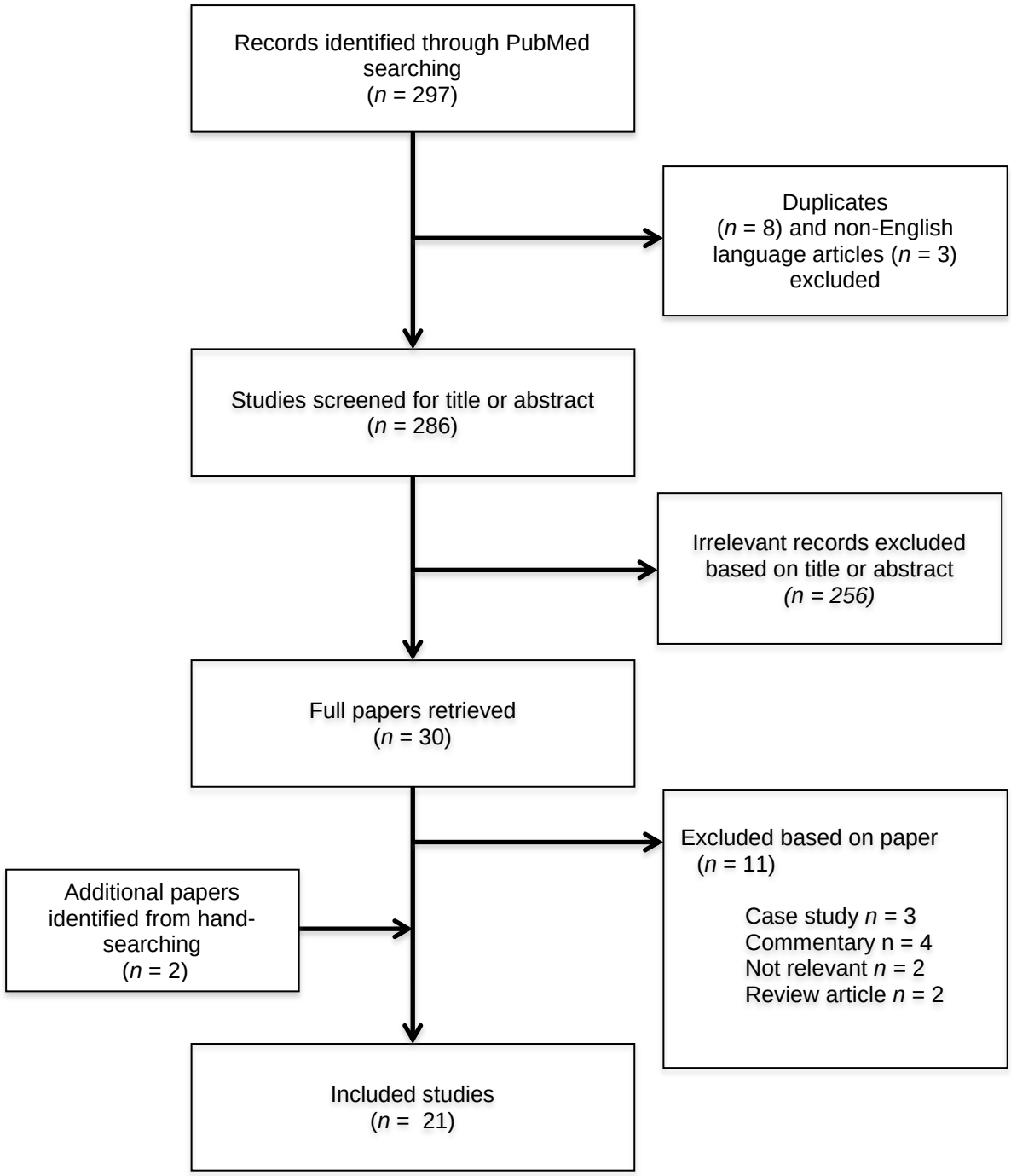

Figure 2

Tables

Table 1 | Third stage of selection of potential routes of administration: inclusion criteria

			Inclusion criteria	
NAME	**DEFINITION**	**FDA CODE**	**Suitable for overdose crisis situation**	**No risk of compromise from overdose complication**
BUCCAL	Administration directed toward the cheek, generally from within the mouth.	030	**X**	**X**
NASAL	Administration to the nose; administered by way of the nose.	014	**X**	possible impairment due to O/D vomit or secretions
SUBLINGUAL	Administration beneath the tongue.	024	**X**	possible impairment due to O/D vomit or secretions or due to closed mouth
RESPIRATORY (INHALATION)	Administration within the respiratory tract by inhaling orally or nasally for local or systemic effect.	136	not viable as O/D victim not breathing or only shallowly	**X**
With the following routes subsumed into the above four routes:				
OROPHARYNGEAL	*Administration directly to the mouth and pharynx.*	*410*	*absorption likely to be too slow*	*possible impairment due to O/D vomit or secretions*
TRANSMUCOSAL	*Administration across the mucosa.*	*122*		*- as for buccal -*